

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA
MYCLOBUTANIL

SB 950-(not assigned), Tolerance # 51315
Chemical Code #: 2245

Feb. 3, 1987
Updated 3/8/88; 3/16/89; 6/30/00; 9/21/00

I. DATA GAP STATUS

Combined (Chronic/Oncogenicity), Rat:	No data gap, possible adverse effect
Chronic, Dog:	No data gap, no adverse effect
Oncogenicity, Mouse:	No data gap, no adverse effect
Reproduction, Rat:	No data gap, no adverse effect
Teratology, Rat:	No data gap, possible adverse effect
Teratology, Rabbit:	No data gap, no adverse effect
Gene Mutation:	No data gap, no adverse effect
Chromosome Aberration:	No data gap, no adverse effect
DNA Damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Note, Toxicology one-liners are attached

** indicates acceptable study

Bold face indicates possible adverse effect

File name T000921

Revised 3/16/89 by J. Gee; M.; M. Silva, 6/30/00; 9/21/00.

Note: The SRS has not been revised to reflect the change in status of the Gene Mutation studies since Medical Toxicology has already recommended Section 3 registration.

NOTE: ONE-LINERS FOR A REPRODUCTION STUDY AND 4 MUTAGENICITY STUDIES FOR THE PLANT METABOLITE, TRIAZOLE ALANINE, ARE APPENDED AT THE END OF THE SUMMARY.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

The 1986 rat combined study, below, indicated a possible significant adverse effect, testicular atrophy, which had an LEL of 200 ppm and a NOEL of 50 ppm. **No** comparable testicular lesions were observed in the chronic mouse study (Vol. 067, pp. 1402-1403) nor in the chronic dog study (Vol. 072, p. 144). Testicular atrophy was also observed in the rat reproduction study (Vol. 078), however only in the second generation and only at the highest dose tested (1000 ppm). There was a marked correlation between males with testicular atrophy and males which failed to sire offspring in the reproduction study. In the rat oncogenicity study, below (135, 137, 138/122363m 1223366-67) testicular pathology was observed. A chronic NOEL was not achieved in this study. Rat, mouse, and dog studies indicated that the liver is the most commonly affected organ, with “no observed adverse effect levels” of 100 ppm or above. (M. Silva, 6/30/00)

135 (5 volumes), 137 & 138, 122363, 122366 – 67 “RH-3866 Technical (myclobutanil): 104-Week Dietary Oncogenicity Study in Rats,” (Wolfe, G.W.; Hazleton Washington, Incorporated (HWA), Vienna, VA; HWA Study #: 417-471; RH 89RC-260; 2/12/93 & 3/4/93 (Sponsor’s Pathology Peer Review Report)). RH-3866 (myclobutanil technical, 92.9% pure) was fed in diet to Sprague-Dawley, Crl:CD®BR VAF/Plus® at 0 (60/sex; vehicle = acetone), 0 (15/sex sentinel, basal diet only) and 2500 ppm (mg/kg/day = 106.08 ± 31.63 M & 135.62 ± 31.67 F) for 104 weeks. Chronic NOEL < 2500 ppm (Bodyweights were significantly decreased in both sexes. Liver weights and liver/bodyweight ratios were increased (both sexes) and testes and epididymal weights were decreased throughout the study. Liver gross pathology was observed (primarily in males) and testicular pathology also occurred throughout the study. Liver (centrilobular/midzonal hepatocellular enlargement & vacuolization—both sexes) and testicular (arteritis/periarteritis, debris in epididymal lumen, aspermatogenesis, decreased spermatogenic activity, hypospermia) pathology occurred in treated rats.) Oncogenic NOEL > 2500 ppm (There were no treatment-related oncogenic effects.) **Possible adverse effect:** Testicular pathology. Not acceptable and not upgradeable (A chronic NOEL was not achieved and too few doses were used.) M. Silva, 6/28/00.

136 122364 “RH-3866 Technical (myclobutanil): 104-Week Dietary Oncogenicity Study in Rats Report Amendment 1,” Rohm and Haas Company Report #: 89-RC-260C; 3/4/93. This report is an amendment to study 135 (5 volumes), 137 & 138, 122363, 122366 – 67, which has been reviewed by DPR. The amendment contains corrections to the original report, but there is no change in the status of the original study. M. Silva, 9/21/00.

****058-064 051868-74** “Chronic Toxicity and Oncogenicity Study with RH3866 in Rats”. (10/24/86, Tegeris #8342). RH-3866 technical, 2 lots, 90.4% and 91.4% purity stated. 0, 50, 200 or 800 ppm in diet to 110 Sprague-Dawley rats/sex/group (50-58/group for interim sacrifice); NOEL = 50 ppm (possible adverse effect: testicular atrophy in 200 and 800 ppm males). No oncogenic effect noted. Acceptable. C. Aldous, 1/12/86.

CHRONIC, DOG

**072-3 051882-3 “RH-3866: One Year Dietary Study in Beagle Dogs” (10/15/86, Rohm & Haas #84R-078). RH-3866 technical, lot LAP-0298, 91.4% purity, @ 0, 10, 100, 400 or 1600 ppm in diet to 6/sex/group Beagle dogs for 1 year; NOEL = 100 ppm: hepatocellular hypertrophy (both sexes), and increased serum alkaline phosphatase levels (females) at 400 ppm. Signs generally attributable to liver toxicity at 1600 ppm included markedly swollen hepatocytes, increases in SGPT (M), GGT (F), and significantly increased liver weights. Acceptable and complete. C. Aldous, 12/19/86.

ONCOGENICITY, MOUSE

139 (3 volumes) & 140 122368 – 69 “RH-3866: Dietary Oncogenicity Study in Female,” (Anderson, D.M., O’Hara, G.P., Brown, W.R.; Rohm and Haas Company, Spring House, PA; Protocol #: 89P-261; Report #: 89R-261; 3/17/93). RH-3866 (myclobutanil technical, 92.9% pure) was fed in diet to Crl:CD[®]-1(ICR)BR female mice(60/dose) at 0 (Vehicle = acetone) and 2000 ppm (MTD) for 18 months (10/sex/dose were sacrificed at 12 months). Mean dietary intake was 414.0 ± 59.7 (12 months) and 393.8 ± 67.2 (18 months). Chronic NOEL < 2000 ppm (Bodyweights were significantly decreased throughout the 18 months of dosing (2-12% of control) and bodyweight gain was decreased 12-26% of control over 18 months. Food consumption was decreased during the first 2 weeks of study, then intermittently thereafter. There was an increase in mean white blood cell count at 12 and 18 months (statistically significant at 18 months). Absolute and relative liver weights were increased. There was increased liver pathology (hypertrophy, single-cell necrosis, vacuolization & pigmented cells) and adrenal cortical hypertrophy.) Oncogenic NOEL > 2000 ppm (There were no treatment-related oncogenic effects.) M. Silva, 6/28/00.

065-071 051875-81 “Dietary Chronic and Oncogenicity Study in Mice Report # 84R-023.” (10/17/86, Rohm & Haas) RH-3866 technical, lot LAP-0298, 90.4% purity, @ 0, 20, 100 or 500 ppm in diet to 70 COBS CD-1 mice/sex/group for 2 years (additional mice designated for interim sacrifice); NOEL = 20 ppm (increased hepatic MFO activity, particularly in females, at 100 ppm and above). NOAEL = 100 ppm (liver vacuolation, necrosis of individual hepatocytes, other alterations limited primarily to 500 ppm males). No oncogenic response. **Acceptable as an oncogenicity study. (C. Aldous, 01/08/86).

REPRODUCTION, RAT

** 51315-078 051888 “RH-53,866: Two-generation Reproduction Study in Rats.” (8/21/85, Rohm & Haas #84R-117) Myclobutanil, referred as RH-53,866 technical, lot #LSPL 83/0017E, 84.5% a.i. given in diet at 0, 50, 200 or 1000 ppm in diet for 8 weeks before mating and continuous through two mating, gestation, and lactation periods to 2 generations of 25/sex/grp; NOEL for general toxicity effects = 50 ppm (Centrilobular hepatocytic hypertrophy extended to 200 ppm in males, and more generalized liver toxicity in males and females at 1000 ppm). NOEL for reproductive effects = 200 ppm (testicular and prostate atrophy at 1000 ppm; reduced pregnancy rate [associated with male lesions noted above], slightly increased incidence of stillborn fetuses, and retarded growth of pups during lactation were observed in 1000 ppm

group). Acceptable C. Aldous 1/13/87

TERATOGENICITY, RAT

** 077 051887 "Teratology Study with RH-53,866 in Rats. (6/22/84, Rohm & Haas #83R-024) Myclobutanil technical, lot #83-0017E, 84.5% a.i.) at 0, 31.3, 93.8, 312.6, 468.9 mg/kg by gavage on days 6-15 of gestation to 25 Sprague-Dawley rats/group; maternal toxicity NOEL = 93.8 mg/kg, increased incidence of clinical observations; Developmental toxicity NOEL = 31.3 mg/kg, decreased Viability Index at 93.8 and above, increased incidence of skeletal variants at 312.6 and above. Acceptable Possible adverse effect since developmental toxicity NOEL < maternal toxicity NOEL. J. Parker, 1/7/87.

TERATOLOGY, RABBIT

** 075 051885 "Teratology Study with RH-53,866 in Rabbits." (11/15/84, Rohm & Haas Rept.#83R-217) JAP 1/8/87 Myclobutanil RH-53,866 technical, lot #LAP-0298, 90.4% purity given at 0, 0 (vehicle & water), 20, 60 or 200 mg/kg oral gavage day 7-19 gestation to 18 NZW rabbits/group; maternal toxicity NOEL = 20 mg/kg (weight gain); Developmental toxicity NOEL = 60 mg/kg (increased number of resorptions); no teratogenic effect was observed. Acceptable Parker, 1/8/87.

GENE MUTATION

** 104, 113 064990, 072626, 072630, 067928 "Microbial Mutagen Test." (Rohm & Haas, 82R-193, 1/11/83) RH-53,866, >99%, lot # RP08154-5; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without rat liver activation by plate incorporation assay; concentrations of 0, 75, 250, 500, 750, 1000, 1500, 2500, 5000 or 7500 ug/plate; decreased colony counts at higher concentrations in all strains; no increase in reversion rate reported. Initially reviewed as unacceptable by Gee, 2/26/88, based on inadequate protocol, no individual plate counts, no positive control without activation. Upgraded to acceptable status based on additional submissions of supplemental data in 113 containing protocol and individual plate counts. Gee, 3/16/89.

** 104, 113 064991/064992, 072626, 072630, 067928 "Microbial Mutagen Test." (Rohm & Haas, 83R-162, 10/19/83) RH-53,866, 84.5%, Lot LSPL83-0017E, with RH-964, 6.5% (not identified); \pm S9 from rat liver at 0, 75, 250, 500 750, 1000, 2500 or 7500 ug/plate; four strains of Salmonella; initially reviewed as unacceptable by Gee, 2/26/88, based on the number of plates per concentration not included, no individual plate counts. No increase in reversion rate, repeat trial with TA100. Upgraded to acceptable status based on additional submissions of supplemental data in 113 containing protocol and individual plate counts. Gee, 3/16/89.

** 079, 113 050948, 072626, 072630, 067928 "Microbial Mutagen Tests - Ames." (Rohm & Haas, 83R-256, 1/31/84) Myclobutanil, 90.4% technical, Lot LAP-0298; \pm S9 from rat liver at 0, 75, 250,

750, 2500 or 7500 ug/plate in triplicate, single trial, no evidence for mutagenicity, cytogenicity at high dose conc.; initially reviewed as unacceptable by Gee, 12/17/86, based on a single trial. Upgraded to acceptable status based on change in guidelines in 1987 and additional submissions of two additional studies and supplemental data in 113 containing protocol and individual plate counts. Gee, 3/16/89.

** 079 051889 “RH-53,866 Technical CHO/HGPRT Gene Mutation Assay.” 5/29/84, Rohm and Haas #84R-046) Myclobutanil, 81.%; Rally 40W; tested -S9 0, 25, 60, 80, 85 or 90 ug/ml, 18-20 hours; + rat liver S9, 1 mg protein per ml, at 0, 120, 150, 155, 160 170 or 175 ug/ml, 5 hours; 8 day expression; also, tested 0.3 and 2.0 mg S9 protein/ml at 160 ug/ml; No mutagenic effect; Acceptable Gee, 12/17/86.

CHROMOSOME ABERRATION

079 051893 “Dominant Lethal Study of RH-3866 Administered Orally via Gavage to Crl:COBS CD(SD) BR Male Rats.” (10/10/86, Rohm and Haas #86RC-0054) Myclobutanil, 91.4% 25 males/group given vehicle, 10, 100 or 735 mg/kg by oral gavage; mated 1:2 females for 8 weekly periods; no dominant lethal effect. Unacceptable (no positive control data - request submission of historical data, if available). Gee, 12/18/86.

079 051890 “Chromosome in vivo cytogenetics.” (7/23/84, Rohm & Haas #84R-074) Myclobutanil, technical, 81.5% given orally in a single dose at 0, 65, 260 or 650 mg a.i./kg to 30 male mice per group with sac at 6, 24 + 48 hours of 10/group; also, 5 daily doses to 10 males/group with sac 6 hours after 2nd dosing. No evidence for increased incidence of aberrations. Unacceptable (use of males only, no evidence for MTD or marrow toxicity. Gee, 12/17/86.

**080 051891 “Mutagenicity Evaluation of RH-3866 Technical in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells.” (4/85, Litton [R & H #84P-489]). Myclobutanil referred as RH-3866 technical, lot #83159, 91.9% a.i., duplicate CHO cultures were incubated for 2 hours at 20, 30, 40 or 50 ug/ml with activation or 25, 50 or 75 ug/ml without activation for 17.5 hours; no increase in chromosome aberrations reported Acceptable. No repeat trial. Gee, 12/86.

** 51315-104 064993 “RH-3866: In vivo Cytogenetics Study in Mice.” (Rohm and Haas, 10/30/87, Report No. 87R-141) RH-3866, 91.4% ai; given by oral gavage at 0, 117, 585 or 1170 mg ai/kg (corrected for purity); groups of 7/sex were sacrificed at 6, 27 and 51 hours after treatment with metaphase spreads from 5/sex in the high dose groups being scored, 50 spreads per animal; TEM as positive control; high dose was approximately the LD10; 6 females and 1 male died in the high dose group; no increase in chromosomal aberrations were reported in the high dose group; Acceptable. Gee, 2/26/88.

DNA DAMAGE

**081 051892 “RH-53,866 Technical In vitro Unscheduled DNA Synthesis Assay.” (7/22/86, Rohm & Haas #86R-084) Myclobutanil, 91.9% technical, lot #83159-5; rat hepatocytes at 0, 0.1, 0.5, 1.0, 5.0 or 10.0 ug/ml, scored 50 cells from each of 3 coverslips; no net increase in grain counts; Acceptable Gee, 12/18/86.

TRIAZOLE ALANINE ONE-LINERS (following studies were supported by producers of 4 pesticides, including Rohm and Haas)

Studies on plant metabolite of fungicide, triazole alanine, tolerance # 50434.

REPRODUCTION, RAT

010 - 012 049706 - 049708 Title: Triazole alanine, two-generation study in the rat. (Imperial Chemical Industries, 8/19/86) JG, 12/19/86. Triazole alanine, 97.6%, Batch #TLB 1207/018-024 from Bayer A G; 15 males and 30 females per group were fed 0, 500, 2000 or 10,000 ppm (1%) for 2 generations, 2 litters per generation; diets corrected for purity - analysis of diets over the study indicated the mean for 10,000 ppm to be 9586 ppm; dose selection was based on a preliminary study - high dose was selected so nutrition was not compromised; no adverse effects, reproduction NOEL = 2000 ppm based on slightly lower pup weight at day 1 in F1B, F2A and B litters at high dose; parental NOEL \geq 10,000 ppm; complete report but unacceptable to fill data gap for parental compound. Otherwise, follows guidelines.

GENE MUTATION

009 049705 Title: Salmonella/mammalian Microsome Mutagenicity Test, CGA 131013 Technical. (Ciba-Geigy, 7/11/86) JG, 12/19/86. Triazole alanine, Technical, 97.4%; tested with strains TA1535, TA1537, TA98, TA100 and TA102 with and without rat liver activation, 0, 20, 78, 313, 1250 or 5000 ug/plate, triplicate plates, two trials; no evidence for increase in reversion rate. Not acceptable to fill data gap for parental compound but performed in an acceptable manner.

009 049702 Title: Point Mutation Test with Chinese Hamster Cells V79 (Triazolylalanine.) (Ciba-Geigy Limited, Switzerland, 7/11/86) JG, 12/18/86. Triazolylalanine, 97.4%, tested with and without activation at 0, 500, 1000, 2000, 4000, 6000, 8000 or 10,000 ug/ml; 21 hours -S9, 5 hours +S9; two trials; no increase in mutation frequency; complete but not acceptable for data gap for parental compound. Study was, however, conducted in an acceptable manner.

CHROMOSOME ABERRATION

009 049704 Title: Micronucleus Test (Chinese Hamster) (CGA 131013 Technical.) (Ciba-Geigy, Switzerland, 7/11/86) JG, 12/18/86. Triazole alanine, 97.4%; given by gavage to 24/sex at 0 or 5000

mg/kg with sacrifice of 8/sex/group at 16, 24 and 48 hours; 5000 mg/kg stated the “highest applicable” dose with no explanation; scored a total of 1000 cells for micronuclei; unacceptable (dose selection - some evidence of MTD or bone marrow cytotoxicity must be demonstrated; 5000 mg/kg does constitute a limit test dose for some test types but not this one, therefore, a no-test.)

DNA DAMAGE

009 49703 Title: Autoradiographic DNA Repair Test on Rat Hepatocytes (CGA 131013 Technical.) (Ciba-Geigy, Switzerland, 7/11/86) JG, 12/18/86.

Triazole alanine, 97.4%; tested with primary rat hepatocytes at 0, 0.08, 0.4, 2 or 10 mg/ml, 5 hours; counted 150 cells per concentration, 50 from each of three slides; no evidence for unscheduled DNA synthesis. Complete and acceptable but does not fill data gap for parental compound.

NEUROTOXICITY

Not required at this time.

